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Citation for published version (APA):

Provoost, V., Tilleman, K., D'Angelo, A., de Sutter, P., de Wert, G., Nelen, W., Pennings, G., Shenfield, F., & Dondorp, W. (2014). Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment. *Human Reproduction*, 29(3), 413-417. <https://doi.org/10.1093/humrep/det463>

Document status and date:

Published: 01/03/2014

DOI:

[10.1093/humrep/det463](https://doi.org/10.1093/humrep/det463)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

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Beyond the dichotomy: a tool for distinguishing between experimental, innovative and established treatment[†]

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Submitted on November 15, 2013; resubmitted on November 15, 2013; accepted on November 25, 2013

STUDY QUESTION: The precise delineation of the research phase is a recurrent subject of debate: When is the evidence base firm enough to decide that a new technology or treatment no longer needs to be regarded as 'experimental'?

SUMMARY ANSWER: We propose a framework that distinguishes between three instead of two types of treatment and describes a continuum from experimental over innovative to established treatment, offering a tool meant to facilitate decision-making about the introduction of new technologies in the clinic.

WHAT IS KNOWN ALREADY: Traditionally, guidelines from medical societies on the notion of 'experimental treatment' depart from a dichotomy between experimental and established treatment. However, in the field of reproductive medicine, there are several problems with a dichotomous framework. First, it does not offer an adequate account of the reality in the clinic. Secondly, this view may bring about several negative effects for the patient, such as techniques being considered established too early, holding risks unknown to patients. A further drawback of the dichotomy is that if a technique is no longer considered experimental, centres offering the technique may no longer consider it useful gathering and critically examining (follow-up) data.

STUDY DESIGN, SIZE, DURATION: The framework and scoring tool were developed over several phases during which the authors operated as a consensus group of experts.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The scoring tool reflects the continuous progression of a new procedure from experimental through innovative to established. For this evolution, four criteria were considered relevant. The first (efficacy) is a categorical criterion (pass/fail). The other three criteria (safety, procedural reliability and transparency and effectiveness) are ordinal in nature. Thresholds have been introduced for all four criteria to avoid that a technology scoring high on procedure and effectiveness but extremely low on safety could move to the next level because of a sufficiently high overall score.

MAIN RESULTS AND THE ROLE OF CHANCE: Only treatments that are rated above the thresholds for all four criteria could be considered at least innovative treatments. When they score 4 or higher on the last three criteria, they are considered established treatments.

LIMITATIONS, REASONS FOR CAUTION: Knowledge about the procedures or techniques under discussion is essential in order to use the tool.

WIDER IMPLICATIONS OF THE FINDINGS: The tool is designed to be used on a macro-level (e.g. by professional societies) although it could also be valuable in the local setting. Both the framework and the tool can bring more clarity on the notion of 'experimental treatment', especially with regard to how to decide when a specific technology or treatment falls in this category and when it can move into one of the other categories.

[†]ESHRE pages content is not externally peer reviewed. The manuscript has been approved by the Executive Committee of ESHRE.

STUDY FUNDING/COMPETING INTEREST(S): none.

TRIAL REGISTRATION NUMBER: none.

Key words: investigational therapies / reproductive medicine / patient safety / follow-up studies / research ethics committees

Introduction

In the rapidly evolving field of reproductive medicine, the introduction of new technologies or treatments is common practice. Ideally, this introduction is preceded by scientific research into the efficacy and the safety of the intervention. During this research phase any clinical application of the technique would be considered experimental, meaning that it should only be offered in a research setting and with approval of a medical research ethics committee. However, the precise delineation of this research phase is a recurrent subject of debate. When is the evidence base firm enough to decide that a new technology or treatment no longer needs to be regarded as 'experimental'? Obviously, this is not just a semantic debate, as much will depend on this label not just in terms of how patients should be informed and counselled, but also in terms of organizational challenges and funding opportunities. A recent instance of this debate turned on whether oocyte vitrification (a new technology which makes it possible to effectively cryopreserve human oocytes) should still be regarded as experimental or whether enough is known about its efficacy and safety to lift this label and allow the technology to be offered to patients as established treatment (Noyes et al., 2010; Gosden, 2011; ESHRE Task Force on Ethics and Law, 2012). This debate occasioned ESHRE's Executive Committee to flag the need for more clarity on the notion of 'experimental treatment', especially with regard to how to decide up to what point a specific technology or treatment needs to be regarded as falling in this category. The special interests groups 'Safety & Quality in Assisted Reproductive Technology' and 'Ethics & Law' have considered this issue and drawn up the present document.

In 2008, the American Society for Reproductive Medicine (ASRM) had defined 'experimental procedures' as follows:

A procedure for the treatment of infertility is considered experimental until there is adequate scientific evidence of safety and efficacy from appropriately designed, peer-reviewed, published studies by different investigator groups (ASRM, 2008).

In their 2009 and 2013 revision, the ASRM specified this level of adequate scientific evidence required to lift the label of 'experimental' for new procedures (ASRM, 2009; ASRM, 2013). In the 2013 paper it was described as 'the published medical evidence regarding their risks, benefits, and overall safety and efficacy is sufficient to regard them as established medical practice' (ASRM, 2013, p. 1197). According to this statement, procedures are thus either considered established medical practice or experimental; the latter requiring specific review of an Institutional Review Board (ASRM, 2008).

In a recent statement replacing the recommendations on ovarian tissue and oocyte cryopreservation issued in 2008, the Practice Committees of the ASRM and the Society for Reproductive Technology (SART) have announced that oocyte vitrification is no longer to be considered

experimental (ASRM and SART, 2013). It is stated that there is sufficient evidence on the safety and efficacy of egg freezing in order to remove the label 'experimental'.

The ASRM statements depart from a dichotomy between experimental and established treatment. However, there are several problems with such a conceptual framework. First, it does not offer an adequate account of the reality in the clinic. Many fertility centres offer treatments to patients that are neither considered established medical treatment, nor regarded as experimental. Secondly, this view may bring about several negative effects for the patient. On the one hand, considering all procedures that are not yet established as experimental would imply that these procedures can only be performed with the specific review of a medical research ethics committee. As this may impact local availability, this could leave patients in the cold waiting for a treatment they could benefit from. On the other hand, the opposite may also be the case: techniques that are considered established too early, may sometimes hold risks unknown to patients. For instance, patients undergoing assisted reproduction techniques (IVF) with preimplantation genetic screening a decade ago may have been exposed to a technology that lowered rather than enhanced their chances of pregnancy (Geraedts and De Wert, 2009). A further drawback of the dichotomy is that if a technique is no longer considered experimental, centres offering the technique may no longer feel the obligation to gather and critically examine (follow-up) data about their patients, which holds risks on long-term safety of patients and children.

In this paper, we offer an alternative conceptual framework as well as a tool meant to facilitate decision-making about the introduction of new technologies in the clinic. The framework that we propose here distinguishes between three instead of two types of treatment and describes a continuum from experimental over innovative to established treatment.

It should be noted that the use of the term 'innovative' in our proposed framework diverges from how this label is sometimes used in the literature, namely to identify a category of innovations that have not (yet) been subjected to scientific research (Dondorp and de Wert, 2011). For instance, this is how, in a recent document of the American College of Obstetrics and Gynecology (ACOG), a distinction is made between formal research (experimental treatment) and practice adaptations by individual practitioners aimed at benefitting their patients (innovative treatment). The ACOG stresses that a practitioner should move such 'innovative treatment' into formal research 'if the innovation represents a significant departure from standard practice, if the innovation carries unknown or potentially significant risks, or if the practitioner's goal is to use data from the innovation to produce generalizable knowledge' (ACOG, 2006, p. 1589).

Whereas in this understanding, 'innovative treatment' refers to a phase that may precede the formal research phase of 'experimental' treatment, in our proposal it refers to an intermediate phase between 'experimental' and 'established treatment'.

Materials and Method

The conceptual framework and the scoring tool presented in this paper were developed over several phases during which the authors operated as a consensus group of experts. During the first meeting, the conceptual framework was set up and criteria for the different types of treatment were defined. In a second meeting, the framework was refined and a preliminary version of the scoring tool was outlined. Next, draft versions of the scoring sheet and scoring key were developed by the first two authors and finalized by consensus in a third meeting.

The scoring tool reflects the continuous progression of a new procedure from experimental through innovative to established. For this evolution, four criteria were considered relevant. The first (efficacy) is a categorical criterion (pass/fail). The other three criteria (safety, procedural reliability and transparency and effectiveness) are ordinal in nature. Thresholds have been introduced for all four criteria to avoid that a technology scoring high on procedure and effectiveness but extremely low on safety could move to the next level because of a sufficiently high overall score.

Results

From experimental to established: three categories of treatment

In our proposal, a procedure is to be viewed experimental, innovative or established based on the four criteria described above.

Experimental treatment

A new procedure can be offered to patients in an experimental design aimed at showing proof of principle (efficacy), short-term safety and/or effectiveness. Providing an experimental treatment requires a commitment to gather evidence regarding safety (for both patient and embryo) and effectiveness. Preferably, there should be studies showing that the experimental treatment is safe in animals. Treatments involving laboratory procedures can be offered when there is at least clinical embryology data that indicate normal cleavage, embryo morphology and blastocyst formation. Experimental treatment should always be embedded in a research setting, in which it is offered to a selected and limited patient cohort. This requires the approval of a local ethics committee, and informed consent of the patient. Patients should be clearly and neutrally informed of the experimental status and should receive information about (the lack of knowledge about) possible risks, alternative treatments etc.

Innovative treatment

An intervention can be considered innovative treatment when data from experimental treatment, although still limited: (i) have shown proof of principle (efficacy); (ii) are reassuring both in terms of safety (in comparison to children conceived by standard treatment, e.g. regular IVF) and effectiveness, (iii) are based on a procedure specified in sufficient detail and with limited technical variability between separate studies. Furthermore, these data must have been (a) obtained in studies with sound methodologies, and (b) published in peer-reviewed journals.

Innovative treatment requires that all conditions applying to experimental treatment have been fulfilled, next to a number of additional conditions. Preferably, the safety of a new laboratory procedure has been shown in studies reporting on its use in animals as well as preclinical data indicating normal cleavage, embryo morphology and blastocyst formation in humans. Furthermore, there should be reassuring data on short-term safety, referring to the patients undergoing the procedure as well as to any children born as a result. These data should be based on experiments with sufficient statistical power. If possible, studies should have been conducted aimed at demonstrating

effectiveness by comparing the new technology with standard treatment. For a treatment to move from innovative to established, the level of evidence required should be higher (see below).

Patients to whom innovative treatment is offered should be provided with clear information about the fact that although the treatment is no longer considered experimental (meaning that there are some data indicating short-term safety and effectiveness of the treatment), the body of evidence is still limited and especially data on long-term effects are lacking. In contrast to experimental treatment, no specific approval of a local ethics committee is needed in order to offer innovative treatment to patients.

Providing innovative treatment implies a commitment to gather further evidence about mid-term safety and effectiveness on all patients to whom the treatment is offered and for as long as the intervention is not considered established treatment. The data gathered by the centre should be made available to the scientific community in the form of peer-reviewed publications, regardless of the success of the treatment: not withholding results that point to a negative outcome or that turn out to be inconclusive.

Centres should systematically and uniformly collect data on procedures and outcomes. Moreover, follow-up studies monitoring the health of patients and children should still be conducted in order to gain more evidence about the longer term safety of the procedure. This of course requires a research protocol, ethics committee approval and informed consent of research subjects.

Established treatment

A treatment is considered established or standard therapy when multi-centred data are published in peer-reviewed journals, on the basis of which it is regarded as a safe and effective therapy. Ideally, this should be based on prospective randomized trials. Established procedures are performed according to a standard and validated protocol.

However, follow-up is still required in order to monitor long-term (ideally transgenerational) health effects, including aspects such as fertility, oncology and mental health. Once a treatment is offered, it is the responsibility of the centre to systematically collect treatment and outcome data that provide a basis for such continued and long-term evaluation. Moreover, clinics should always be prepared to invalidate treatment when proved problematic (in terms of safety or effectiveness).

The path to established therapy: a tool to situate a procedure along the continuum

In order to situate a treatment on the continuum from experimental through innovative to established, it is important to consider the four criteria based on (at least some reports of) research published in peer-reviewed journals: efficacy, safety, procedural reliability and transparency and effectiveness. Figure 1 presents a sequential four-criterion tool to assess specific treatments or technologies. For each of the criteria a threshold is indicated. Once a treatment scores below the threshold for one of the criteria, it cannot be viewed as innovative even though it would score high on subsequent criteria. Only treatments that are rated above the thresholds for all four criteria could be considered at least innovative treatments. When they score 4 or higher on the last three criteria, they are considered established treatments.

In an ideal situation, the sequence of the proposed categories could be viewed as divisions on a continuum, with procedures moving from experimental to established over time. In this way, innovative treatments would be preceded by at least a limited experimental phase. The further a procedure moves on the continuum, the more will be known about its safety and effectiveness while the procedural variability will decrease.

In order to situate a treatment on the continuum, it is important to consider the four criteria based on (at least some reports of) research published in peer-reviewed journals. Each of the criteria should be scored according to the scoring key outlined in Table 1. In order to do so, a significant level of

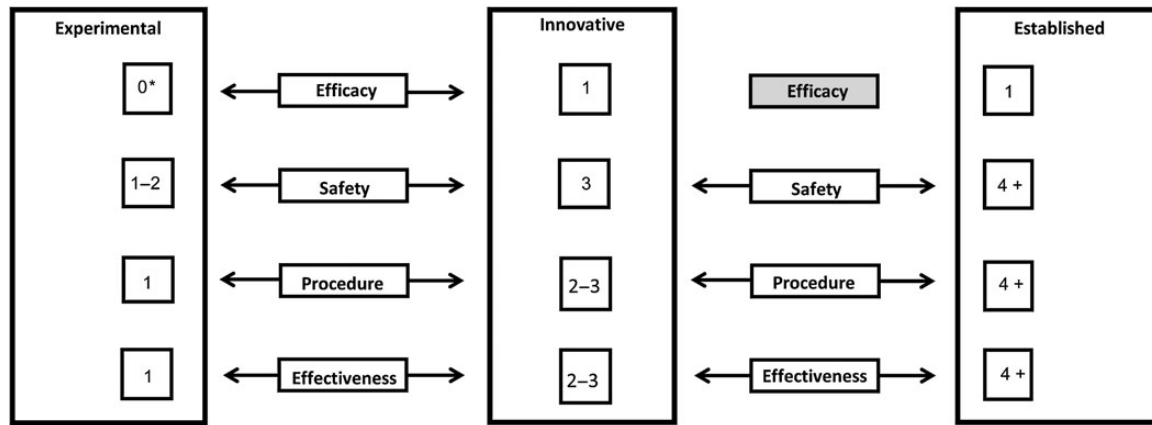


Figure 1 Sequential four-criterion assessment tool to consider the transition of a treatment from experimental through innovative to established. *Numbers represent the scores at either end of the threshold for each of the four criteria for the first transition (from experimental to innovative) and for each of the three last criteria for the second transition (from innovative to established).

Table 1 Scoring key used in the tool for distinguishing between treatments.

Criterion	Definition	Scoring
Efficacy	Proof of principle	0: No proof of principle has been demonstrated 1*: Proof of principle has been demonstrated
Safety	The safety of the procedure, referring to the patients as well as the future children	1: Considered safe in animals 2: Reassuring preclinical data 3*: Reassuring short-term data in human (up to at least 3 months post-delivery) in peer-reviewed journals 4**: Reassuring mid-term data in human (up to at least 5 years post-delivery and including data on psychological development) in peer-reviewed journals 5: Reassuring long-term data in human (up to at least 25 years post-delivery, including data on psychological development and preferably on fertility) in peer-reviewed journals
Procedure	Procedural reliability and transparency: the similarity or variability of the procedure in different laboratories and the potential for implementation by other centres	1: No procedure has been described yet, or the procedure varies enormously between laboratories 2*: Technical performance of the procedure is highly variable between laboratories 3: Technical performance of the procedure is relatively comparable between laboratories 4**: Technical performance of the procedure is highly comparable between laboratories 5: Throughout different centres, the procedure is considered a routine technique with common technical performance
Effectiveness	The likelihood of producing the desired outcome compared with outcome of conventional, established ART techniques	1: Completely unknown, doubtful or extremely low 2*: Low 3: Reasonable 4: Acceptable but not as high as established ART treatment 5**: As high or higher than established ART techniques

An example of an established treatment is IVF.

ART, assisted reproduction techniques.

*Threshold for innovative treatment.

**Threshold to move from innovative to established treatment for the criteria 'safety', 'procedure' and 'effectiveness'. 'Efficacy' is an all-or-nothing criterion that only has one threshold (1, to move from experimental to innovative treatment).

knowledge is required about the treatment or procedure (including recent literature on the topic).

Given that our account of three phases is an ideal model, the continuum should be treated in a flexible way, so as to realistically reflect the

development of techniques in practice. For instance, it is possible that, for a certain procedure, there was no distinct experimental phase. Sometimes, practice rather than research has led to sufficient data on which a decision can be made to regard a new technology or treatment as innovative rather

than experimental. The introduction of oocyte vitrification is an example of this. Also, an innovative treatment could be (and should be) invalidated when found unsafe, ineffective or otherwise problematic. In that case, it would not move forward along the continuum.

Conclusion

Clarifying the boundaries between research and treatment and identifying the distinctions and gradations between them can benefit patients both directly (by way of safeguarding the possibility of offering chances as well as minimizing the exposure to risks and negative effects) and indirectly (through the advancement of medicine and the contribution of data to a growing body of knowledge).

The framework offered in this paper is new in that it includes a category of 'innovative treatment' as intermediate between 'experimental' and 'established'. In addition, we provide a tool to facilitate the discussion and reach an agreement about the classification of treatments for infertility. The tool is designed to be used on a macro-level (e.g. by professional societies) although it could also be valuable in the local setting. Of course, experts may vary in their evaluation of specific techniques. This is not necessarily problematic, it would rather indicate a need to debate the matter and would show that a narrow (or dichotomous) classification of techniques is not desirable. Knowledge about the procedures or techniques under discussion is essential in order to use the tool. Therefore, it is recommended to use the tool by assembling a group of recognized experts on a specific topic and have them scoring the technique. Alternatively, its application could be based on a systematic review of the literature.

Both the framework and the tool can bring more clarity on the notion of 'experimental treatment', especially with regard to how to decide when a specific technology or treatment falls in this category and when it can move into one of the other categories.

Recommendations

Experimental treatment

- (1) Centres offering experimental treatment should do so only after approval by a medical research ethics committee.

Innovative treatment

- (1) Only centres with expertise about the procedure should offer innovative treatment to their patients.
- (2) Centres offering innovative treatment should make a commitment to closely monitor their practice by conducting follow-up studies with the purpose of publishing the (positive and negative) results in peer-reviewed journals. For these studies a formal approval of a medical research ethics committee must be obtained.
- (3) Patients interested in innovative treatment should be adequately informed about all relevant aspects of the procedure and about the status of the treatment. This means that patients should be informed about the innovative character of the treatment meaning that there is only limited information available about children born after this procedure and data on long-term safety still need to be gathered.
- (4) Patients interested in innovative treatment should also be informed about the centre's commitment to monitor the practice. Before the

onset of treatment, these patients should also be asked for their consent to be contacted in the future for follow-up studies.

- (5) Centres offering innovative treatment should always be prepared to stop treatment when there are signs of serious concern based on their own studies or on published reports.

Established treatment

- (1) Centres should take steps to facilitate a uniform data collection (registries) with the aim of enabling studies to evaluate long-term (including multigenerational) consequences.
- (2) Clinics should always be prepared to stop treatment when proved problematic (in terms of efficacy, safety or effectiveness).

Authors' roles

During several consensus meetings, all authors contributed to the design of the framework and the figure as well as to the selection and definition of the criteria and thresholds in the scoring key. V.P. and K.T. created the first drafts of the text and the figure and revised them according to the comments made during the meetings. All authors commented on these drafts and approved of the final version.

Funding

This work was funded by the European Society of Human Reproduction and Embryology (ESHRE).

Conflict of interest

No conflict of interests declared.

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